Effect of striatal and extrastriatal D_2-receptor BP on memory and symptoms of schizotypal personality disorder

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Thesis completed in partial fulfillment of the requirements of the Honors Program in the Psychological Sciences

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Vanderbilt University

April 2007

Approved _____ Date _____

Acknowledgments

First and foremost, my eternal thanks to Dr. David H. Zald. From his incomparable command of the dopaminergic system to his deft ability to anthropomorphize machinery, he has never ceased to amaze me. I doubt that I can fully articulate my gratitude for his patient guidance and encouragement throughout this project. Additional thanks to Evan Shelby for surrendering his use of 'Max'—the preferred computer in the lab—at a moment's notice without complaint, and for assisting me tremendously with the measures used in this analysis, as well as helping me to obtain the data necessary to complete it (often by scoring it himself). My sincerest thanks to other members of the lab who have offered me their sympathy and friendship: particularly to Stephanie Douglas for providing me with the support and good humor necessary to survive otherwise lonely evenings as well as teaching me the imperative skill of composing tables in Excell. I would also like to acknowledge Rui Li and Craig Smith, both for having repeatedly assisted me in spite of my mistakes.

Also, although they did not help me with this project per se, I would like to acknowledge Dr. Caleb Clanton, a perceptive soul and deeply cherished friend, whose insights have occasionally left me staggering (ironically by providing me with an epistemic balance that I had not thought previously possible), and Dr. Roosevelt Noble, whose boundless compassion and keen intellect have harmonized beautifully to provide me with an enhanced understanding of both myself and others. Distinctive thanks to Corwyn Ellison for making my life lovelier each day that she is in it. Finally, of course, I thank my loving parents, for providing me with the courage to regain my ground after every stumble.

Abstract

The integrity of particular dopaminergic projections via the striato-thalamic-cortical feedback loop potentially influences specialized aspects of cognition and psychopathology. Research has identified a role for striatal D2 receptors in the cognitive impairments and psychopathological symptoms associated with disorders of the schizophrenia spectrum. Recent developments in PET neuroimaging methods currently permit visualization of D_2/D_3 receptors in extrastriatal regions. This study evaluated potential correlations between the regional D_2/D_3 receptor BP in striatal and extrastriatal areas and psychopathological symptoms and memory performance. Significant correlations were observed between particular regions of D_2/D_3 receptor BP and both verbal and visual memory sub-scales of the Wechsler Memory Scale-III.

Effect of striatal and extrastriatal D_2-receptor BP on cognitive performance and symptoms of schizotypal personality disorder

Several PET and SPECT studies with human subjects have implicated striatal D2 receptors in cognition and symptoms of psychopathology (Reeves et. al., 2005; Abi-Dargham, 2004; Hirvonen et al., 2005; Schneier et al., 2000). However, models of the dopamine (DA) system, based largely on studies of rodent and non-human primate cortex, suggest that particular cortical sites differentially affect striatal D_2 receptor expression and activity (Deutch, 1992; Weinberger, 1987). Therefore, an analysis that considers the binding potential (BP) of D_2 receptors in both cortical and striatal structures may better predict performance on cognitive tasks and manifested symptoms of psychopathology. Studies of D_2 receptor activity in the living human brain have been restricted to the striatum due to an inability to quantify the more sparsely innervated cortical structures. However, the development of high-affinity radioligands such as [^{11}C] FLB 457, [^{123}I] epidepride, and [^{18}F] fallypride currently allows quantification of D_2 receptor populations in extrastriatal regions (Mukherjee et al., 2004). Of these radioligands, only [^{18}F] fallypride allows the simultaneous analysis of striatal and extrastriatal D_2 receptor BP with PET in vivo (Mukherjee et al., 2004, Riccardi et al., 2005). The receptor BP of particular cortical and striatal regions may uniquely contribute to performance on cognitive tasks and schizotypal assessments among healthy participants. Moreover, ratios of cortical to striatal D_2 receptor BP may better predict participants' scores relative to isolated regions. If so, the ratio approach could prove fruitful in future research.

Radiotracing studies of rodents and non-human primates have shown that DA neurons in the substantia nigra (SN) possess numerous feedback loops through the striatum and ultimately send projections via the mesocortical DA pathway to medial prefrontal, cingulate, and entorhinal regions, which collectively comprise the limbic cortex (Cooper, Floyd & Robert, 1996, chap. 9; Deutch, 1992; Haber, Fudge, & McFarland, 2000). In addition to receiving projections from the midbrain and striata, each of these cortical regions topographically projects to divisions of the striatum, thereby modulating dopaminergic activity at striatal D_2 receptors (Haber, Fudge & McFarland, 2000). Traditional DA models propose that deficient prefrontal DA reduces the capacity of cortico-striatal projections to regulate subcortical DA activity, thereby increasing the responsiveness of the mesolimbic DA pathway (Deutch, 1992; Weinberger; 1987). Because D_2 receptor antagonists commonly ameliorate positive symptoms, the process described above could underlie positive—or psychotic—symptoms of schizophrenia (Deutch, 1992; Deutch 1990; Cooper, Floyd & Robert, 1996, chap. 9). Although considerable research describes dysfunctional dopaminergic transmission in disorders of the schizophrenia spectrum, D_2 receptor expression and activity has been associated with a variety of cognitive disturbances. Studies of D_2 receptor BP in striatal and cortical regions thereby applies to disorders of the schizophrenia spectrum as well as other neuropsychological conditions and cognitive deficits associated with healthy aging. (Cropley et al., 2006).

Neuroimaging research has just begun to explore the role of extrastriatal D_2/D_3 receptor BP with respect to DA release in human cognition. Using the high-affinity radiotracer [^{11}C] FLB 457 and PET with a sample of healthy male participants, Aalto et

al. (2006) demonstrated regionally-specific changes in extrastriatal D_2/D_3 receptor BP during attention and working memory task performance. More specifically, compared with baseline, D_2/D_3 receptor BP decreased in the left ventral anterior cingulate while participants performed a vigilance task, whereas D_2 receptor BP decreased in the left medial temporal cortex while participants performed a working memory task. Intriguingly, Aalto et al. (2006) also observed trends between changes in the D_2 receptor BP of particular regions and specific aspects of working memory task performance: decreased D_2 receptor BP in the right ventrolateral prefrontal cortex was associated with shorter reaction times, whereas reduced D_2 receptor BP in the left ventral anterior cingulate was associated with a decreased variability of errors. According to the binding competition principle, the findings reported by Aalto et al. (2006) may reflect an increased release of endogenous dopamine in the anterior cingulate and medial temporal cortex while participants performed the vigilance and working memory tasks, respectively. Such evidence compellingly suggests that the regional BP of particular D_2 receptor populations—namely, those located in striatal, temporal, cingulate, and frontal cortices—may uniquely influence specific dimensions of cognitive performance. Another PET study used [^{18}F]fallypride to investigate the effects of $_D$-amphetamine administration on alterations in D_2 receptor BP in extrastriatal and striatal regions and concurrent changes in cognitive task performance (Riccardi et al., 2005). The administration of $_D$-amphetamine, a D_2 receptor antagonist, commonly increases endogenous dopamine release via D_2 receptor binding (and reductions in the BP of the radioligand may therefore reflect increases in dopaminergic transmission). Riccardi et al. (2005) reported significant clusters of negative correlations between changes in the BP of circumscribed D_2 receptor

populations and concurrent changes in cognitive performance on particular tasks among a sample of healthy male and female participants. Regional changes in the D_2 receptor BP of the ventral striatum, the ventral putamen, and the temporal cortex each negatively correlated with altered performance on the Digit Symbol Coding task (an assessment of attention and processing speed), the Symbol Search task (a measure of processing speed) and the Stroop task (an evaluation of attention), respectively (Riccardi et al., 2005). In other words, increased dopaminergic release following $_D$-amphetamine administration was associated with lower scores on these cognitive measures. The D_2 receptor BP of extrastriatal regions therefore demonstrates an evident but heterogeneous relationship with dimensions of human cognition. It is important to add that Riccardi et al. (2005) observed no correlations between $_D$-amphetamine induced changes in D_2 receptor BP and a task assessing working memory. The two studies employed considerably different methodologies, making any comparison speculative at best. More studies that evaluate the relationship between cognitive performance and D_2 receptor BP may further elucidate the role of D_2 receptor function in executive functioning.

Schizotypal Personality Disorder

The relative densities of D_2 receptor populations in particular regions of the brain may contribute to the origin and treatment of symptoms of schizotypal personality disorder (SPD) and associated cognitive disturbances. According to the DSM-IVR, the lives of schizotypal individuals are characterized "by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behavior" (DSM-IV-TR, p. 701). Generally, SPD is characterized by positive (cognitive/perceptual eccentricities), negative (cognitive deficits), and

disorganized (odd speech and behavior) symptoms, although schizotypal individuals exhibit remarkable heterogeneity in the severity and precise constellation of manifested symptoms (Raine et al., 1994; Siever & Davis, 2004; Siegel et al., 1995; Shihabuddin et al., 2001). As with schizophrenia, the onset of SPD usually occurs in early adulthood and its associated symptoms are present in a variety of contexts (DSM-IV-TR, p. 701). Although schizophrenic patients and schizotypal individuals both demonstrate similar neurochemistry, cognitive impairments, and pathological symptoms, schizotypal individuals rarely develop frank psychosis and usually do not require medication (Siever & Davis, 2004).

The role of D_2 receptor function in SPD remains poorly understood. Most neuroimaging studies of patients with schizotypal personality disorder have not demonstrated significant correlations between structural or functional abnormalities in the striatum and the positive, negative, or disorganized symptoms exhibited by schizotypal individuals (Abi-Dargham et al., 2004; Levitt et al., 2002; Shihabuddin et al., 2001). However, Siegel et al. (1996) reported improved performance on the Wisconsin Card Sorting Task—a measure of executive functioning—among the majority of patients within a sample of schizotypal individuals following d-amphetamine administration. Individuals who exhibited the most severe perseverative symptoms during the placebo trial improved the most following $_D$-amphetamine administration. However, because the study did not incorporate neuroimaging methods, these findings do not indicate whether striatal or cortical D_2 receptor BP correlated with improved performance. Abi-Dargham et al. (2004) used SPECT imaging and the radioligand [^{123}I] Iodobenzamide to evaluate potential relationships between schizotypal symptom scores and striatal D_2 receptor BP

following $_D$-amphetamine administration. Researchers reported that $_D$-amphetamine administration improved negative symptom scores but did not influence positive symptom scores within a sample of schizotypal patients. However, improvements in negative symptom scores did not correlate with changes in striatal D_2 receptor quantifications. Considering the afore-mentioned study by Riccardi et al. (2005), associations may exist between the cognitive improvements among schizotypal patients reported by Abi-Dargham et al. (2004) and Siegel et al. (1996) and D_2 receptor BP in extrastriatal regions. This interpretation is tentative, however, and requires further investigation.

Both schizotypal and healthy individuals demonstrate considerable heterogeneity in their density and distribution of D_2 receptors, cognitive performance, and schizotypal symptom expression (Abi-Dargham, 2004; Siegel et al., 1995; Shihabuddin et al., 2001). Therefore, assessments of these variables in a sample of healthy volunteers would likely provide the necessary between-subject heterogeneity to observe the distinct relationships that may exist between regional densities of D_2 receptor populations (as well as striatal to extrastriatal D_2 receptor BP ratios), schizotypal symptom expression, and cognitive task performance. Moreover, potential correlations observed among a sample of healthy participants would offer greater external validity to the results. Finally, the paucity of research concerning schizotypal personality disorder provides a strong impetus for further study of the neurological anomalies that contribute to this illness (Siever & Davis, 2004).

A large body of evidence for current models of cortical dopaminergic transmission originates from studies of rodent or non-human primate cortex (Deutch, 1992; Weinberger, 1987). Such studies have shown that lesions applied to entorhinal

cortices induce striatal D_2 receptor up-regulation and behavioral deficits that resemble some negative symptoms of SPD and schizophrenia (Schmadel et al., 2004; Schneier et al., 2000). Alternatively, lesions applied to prefrontal cortex increase the responsiveness of receptors in the nucleus accumbens, which, in the presence of stress, can elicit overt increases in DA release along the mesolimbic pathway and behavioral disturbances that resemble positive symptoms of SPD and schizophrenia (Deutch, 1992; Weinberger, 1987). These findings suggest that particular cortical regions may uniquely influence the quantity and function of striatal D_2 receptors, thereby modulating specialized aspects of cognitive performance and schizotypal symptom expression. However, obvious discrepancies in the cortical dopaminergic systems of rodents and non-human primates compared with those of humans limit the application of animal models to the human dopaminergic system (Berger, 1992). Analysis of the relationship between the regional BP of D_2 receptors and either cognitive performance or schizotypal symptom expression may clarify the manner in which specific D_2 receptor populations contribute to particular dimensions of cognition and SPD. Furthermore, if striatal to extrastriatal D_2 receptor BP ratios better predict cognitive performance and the manifestations of schizotypal symptoms than isolated populations of D_2 receptors, then a ratio approach to analyses of D_2 receptor anatomy and function may improve our understanding of the human dopaminergic system and its role in both normal cognitive processes and psychopathology.

D_2 receptor densities of temporal and frontal regions likely possess unique relationships with striatal D_2 receptor BP, thereby differentially influencing human cognition and psychopathological symptoms. A recent PET study using [^{11}C]FLB 457

reports that schizophrenic individuals exhibit decreased D_2 receptor BP in the anterior cingulate (Suhara et al., 2002). Moreover, Suhara et al. (2002) observed a significant negative correlation between the BP of D_2 receptors in the anterior cingulate and the positive symptom score on the Brief Psychiatric Rating Scale (BPRS). The D_2 receptor populations in each of these regions (frontal cortex, temporal cortex, and the cingulate) may possess a unique relationship with D_2 receptor BP in the striatum. If such specialized relationships exist, then regional populations of extrastriatal D_2 receptors, combined with measurements of striatal D2 receptor BP, would likely correlate with specific dimensions of cognitive functioning and schizotypal symptom expression.

For this study, two competing hypotheses will be tested using the same data collected from a sample of healthy volunteers. One hypothesis suggests that the ratios of striatal to extrastriatal D_2 receptor populations provide superior predictions of cognitive task performance and schizotypal symptom expression than that of isolated regions, and the other suggests that the D_2 receptor BP of isolated regions better determines cognitive performance and schizotypal symptom manifestation. If data support the first hypothesis, then the inter-regional pattern of D_2 receptors may better predict cognition and psychopathology than regionally-specific levels of receptors.

Methods

Participants

Seventeen healthy individuals (seven women) between the ages of 18 and 32 participated in the current study. Mean age is 24.8. Recruitment occurred through the department of psychiatry research pool and the department of psychology research pool

at Vanderbilt University. Exclusion criteria included high levels of current alcohol use or any use of legal or illegal psychotropic agents within the prior six months, as well as any former or current psychiatric illness as assessed by the Structured Clinical Interview for the DSM-IV (SCID-IV). All participants gave written informed consent and receive monetary compensation for their involvement in the study. The protocol was approved by the Vanderbilt Institutional Review Board.

Apparatus and Measures

PET scan

Time-activity curves were obtained with a whole-body GE Discovery Space LS Positron Emission Tomography (PET) scanner with 4 mm axial resolution and an in-plane resolution of 4.5-5.5 mm FWHM at the center of the camera's field of view. [^{18}F] fallypride was prepared in the radiochemistry laboratory attached to the PET unit, following synthesis and quality control procedures (reverse phase HPLC) described in IND 47,245—the application to the FDA for an investigational drug permit. Radiochemical purity was always >95%. [^{18}F] fallypride was injected with an indwelling catheter.

Quantification of [^{18}F] fallypride binding

All images were re-aligned for motion correction using algorithms based on the maximization of mutual information over a regular grid of splines (Maes et al., 1997). Relative to traditional image registration algorithms—which fail to account for the changing nature of the dynamic signal over time—this technique provided superior registration. Each dynamic scan frame was resampled to 1 mm pixel registration. Serial coregistered PET scans were weighted according to information content and combined to

generate a composite PET image. This composite PET image offered a low noise standard for subsequent co-registrations. The serial dynamic frames were then reregistered to the composite PET images in order to compute model parameters for both region of interest (ROI) and parametric image analysis. PET and structural MRI data were realigned along the AC-PC plane and warped to conform to a template MRI in Talairach space using an intermodality co-registration technique (West et al., 1999). To ensure the quality of registrations, all motion corrections and intermodality alignments were visually inspected.

In this study, a common ROI extraction was performed on individual data. Regional BP levels were calculated with the full reference region method described by Lammertsma et al. (1996). Because of its relative lack of D_2/D_3 receptors, the cerebellum served as the reference region (Hall et al., 1994). Both hypotheses were examined within predefined ROIs, which were determined a priori. The caudate and putamen were chosen because they possess the highest levels of D_2 receptors. Three cortical regions—the temporal, lateral frontal, and temporal cortices—were chosen because of their broad roles in cognition, as well as possessing relatively different D_2/D_3 innervation characteristics. ROIs were averaged together across hemispheres. Using a manual tracing technique, ROIs were drawn on the template MRI to which each participants' PET data is coregistered. The template MRI was first filtered using BrainVoyagerQX (Brain Innovations, Germany) in order to maximize grey-white matter contrast. ROIs were manually delineated on slices of this high contrast image using an in-house image viewer program that allowed simultaneous viewing of the MRI template and the averaged data of all participants' PET images. ROIs were therefore constrained by anatomical boundaries

as well as the participants' averaged receptor characteristics. The PET images had a resolution of 4 mm^3 voxels, whereas the MRI images had a resolution of 1 mm^3 voxels. To account for this discrepancy, investigators applied the nearest-point interpolation method to PET images and maintained a linear interpolation method for the MRI images during ROI delineations, and ROIs were drawn every 4 slices.

The program used to trace ROIs permitted simultaneous assessment of the template MRI and individual PET data. ROIs for the neostriatum were drawn on the coronal plane by tracing gray matter boundaries of the striatum. These ROIs were particularly conservative to avoid partial volume averaging. ROIs for the cingulate were depicted on the saggital plane, drawn on two slices of each hemisphere that fringe the interhemispheric fissure. The boundaries for the cingulate were defined by tracing the cingulate sulcus and the corpus collosum. ROIs for both the temporal and the lateral frontal regions were drawn on the transverse plane. The temporal ROIs included lateral temporal cortex extending from the temporal poles to the occipitotemporal and parietotemporal junctions; at the inferior-most slices, the ROIs extended medially in order to include inferior temporal cortex. Although some of the entorhinal cortex was included in the temporal ROIs, the hippocampus and amygdala were excluded. Generally, Broadmann's areas 9 and 46 were included in the lateral frontal ROIs. The lateral and medial boundaries were determined by the point at which average D_2 receptor binding potential dropped below 0.5, which corresponds to the depths of gray matter in the frontal sulci. Structurally, the superior frontal sulcus served as both the anterior and the medial boundary and the sulcus triangularis constituted the posterior boundary. All ROIs were

visually inspected to assess the precision with which ROIs incorporated the regional D_2 receptor BP of individual participants.

Neuropsychological Testing

Participants performed selected measures of various test batteries in order to assess potentially dissociable aspects of cognitive functioning. A research assistant in Zald's lab administered the Controlled Oral Word Association task (COWA), the Finger Tapping Task (FTT), the Grooved Pegboard (GPB) task, and the Stroop task, in addition to particular subscales of the Wechsler Memory Scale-III (WMS-III) and the Wechsler Adult Intelligence Scale-III (WAIS-III). The WMS-III included all measures within the subscales of Logical Memory, Verbal Paired Associates, and Visual Reproduction, whereas measures from the WAIS-III included the Digit Symbol Coding (DSC) and Symbol Search (SS) tasks. In addition to assessing performance on the separate tasks of Logical Memory and Verbal Paired Associates, the immediate recall measure of the Logical Memory subscale and the delayed recall measure of Verbal Paired Associates subscale were combined to create a verbal memory index score (Auditory Immediate Index) according to the WMS-III Administration and Scoring Manual (1997). According to previous findings, neuropsychological measures therefore evaluated selective attention (Stroop), verbal memory (Verbal Paired Associates and Logical Memory subscales), verbal fluency (COWA), visual memory (Visual Reproduction), processing speed (SS) and motor speed performance (GPB) (Lezak, 1995). Because of time constraints, only the analyses of the visual reproduction immediate recall sub-scale and the Auditory Immediate Index score will be reported here.

To assess the prevalence and severity of particular schizotypal symptoms within a sample of healthy volunteers, experimenters administered the schizotypal personality questionnaire (SPQ). The schizotypal personality questionnaire permitted a systematic assessment of the positive, negative, and disorganized symptoms related to SPD (Park & McTigue, 1997). Factor analysis revealed that the SPQ breaks down into three factors that approximate the afore-mentioned schizotypal symptoms correspondingly: Cognitive-Perceptual, Interpersonal, and Disorganized (Raine et al., 1994). Vollema and Hoijtink (2000) also observed this three-factor structure in psychiatric inpatients and outpatients.

Procedure

Prior to any experimentation, all participants gave written informed consent. Because the data used for the current participants was also used for a separate study of amphetamine response, individuals were pre-screened for amphetamine-related risks as assessed by a physical exam, conducted shortly after psychiatric assessment with the SCID-IV. During this initial screening, an electrocardiogram (EKG) and a structural Magnetic Resonance Imaging (MRI) brain scan were scheduled. Following the EKG and MRI assessments, the PET procedure was scheduled for individuals who remained qualified for participation. On the day of scanning, participants completed all of the cognitive tasks described above except for the Wechsler Memory Scale, which was conducted during a separate testing session.

For assessment with PET, participants were asked to lie supine upon the scanner bed, and their head was positioned within the scanner to allow axial slice collection parallel to the orbitomedial plane. Participants were positioned to ensure that both the superior edge of the cingulate and the inferior temporal cortices were within the camera's

field of view. Dots were placed on the participant's forehead and cheeks for periodic visual checks of alignment throughout the duration of each scan, and for repositioning after breaks. Prior to injection with [^{18}F] fallypride, participants received a transmission scan for attenuation correction using rotating rods of ^{68}G/^{68}Ga. As mentioned above, 5 mCi of [^{18}F]fallypride (specific activity greater than 2,000 Ci/mmol) was injected over a 30-second period. Over the initial hour following injection, 27 serial scans of increasing duration were performed. After the initial set of scans, the participant had a 15-minute break and was encouraged to empty her or his bladder. A second set of scans was subsequently collected over a 50-minute period. A second 15-minute break was then followed by a third set of scans that lasted 40 minutes. This sequence permits data collection over a period of 3.5 hours, which offers excellent measurements of D_2 receptor BP in both striatal and extrastriatal regions. At the conclusion of the PET study, vital signs—blood pressure, pulse, temperature and respirations—were measured and a brief motor neurological examination was performed.

Statistical Analysis

Using SPSS Data Editor 14.0 (SPSS Inc., 1985-2005), a Pearson product moment correlation using two-tailed *t*-tests was conducted to assess the association between the basal BP of [^{18}F] Fallypride BP within manually-delineated ROIs in either extrastriatal to striatal ratios or isolated regions and both the scores for sub-scales of the SPQ or scores derived from performance on cognitive measures. Using the same program, a step-wise multiple regression analysis was performed on the afore-mentioned data. Although the total score on the SPQ demonstrated sufficient variability between subjects, the individual sub-scales (assessing odd, negative, and positive symptoms) did not.

Due to the scarcity of significant correlations obtained using the ROI data, an alternative pixelwise approach was taken to the analysis. Pixelwise statistical parametric maps allow for examination of the correlation at each pixel in the brain, thereby allowing potential correlations to be observed in subregions of a particular area. Whereas ROI analyses may fail to detect correlations if only a part of an area has a correlation, pixelwise analyses do not suffer from this limitation. For this analysis, correction for multiple within-image comparisons was performed using the method of Forman et al. (1995) as implemented in the Alpha-Sim program of the AFNI analysis program. This technique examines the likelihood based on chance of observing a cluster of activation within a given spatial extent. Based on the spatial resolution of the PET BP images, it was determined that a cluster must include at least 50 pixels to be considered to reach a spatial extent criterion of $p<0.05$.

Results

Schizotypal and memory scores are summarized in Table 1 and Table 2, respectively. Tables 3 and 4 depict the D_2/D_3 receptor BP extracted from isolated ROIs and extrastriatal:striatal ROI ratios. Using SPSS Data Editor 14.0 (SPSS Inc., 1985-2005), a step-wise, multiple regression analysis conducted on the D_2/D_3 receptor BP derived from ROI extractions (at both the isolated and ratio level) and scores obtained from participants' cognitive and schizotypal assessments revealed no significant results. Pearson product moment correlations conducted with the same program on participants' SPQ scores and the D_2/D_3 receptor BP derived from ROIs of either extrastriatal to striatal ratios or isolated regions also produced insignificant findings. Upon inspection, the

scores derived from the SPQ sub-scales seemed to lack sufficient between-subject variability, and further analyses exclusively examined potential relationships between D_2/D_3 receptor BP as assessed with [^{18}F] fallypride and performance on memory tasks. Pearson product moment correlations conducted on isolated ROI extractions and these neuropsychological assessments revealed no significant findings. When the same analysis was performed on extrastriatal to striatal BP ratios, no significant associations were obtained. Subsequent analyses investigated correlations revealed by parametric images.

Parametric images of significant (numbers of pixels>50) clusters of continuous pixels that represented correlations between scores on tasks assessing verbal memory and D_2/D_3 receptor BP demonstrated significant findings (Figure 1). Scores on the auditory memory index (which combined sub-scales of logical memory and verbal paired associates tasks) showed a significant cluster of correlations within the banks of the Sylvian fissure near the left temporal pole, with peak pixel correlations reaching r = 0.79 (p<.01) which, using Talairach coordinates (in which a negative value for x is left of the intercommisural plane, a negative for the y value is posterior to the anterior commissure, and a negative value for z is inferior to the acpc plane), was located at x= -58, y= 41, and z= -35) (Figure 1A). A trend correlation cluster was also observed within the right hippocampus, with peak pixels reaching r=.75, p<.01 (x=33, y=32, z=-66); although the magnitude was significant, the number of pixels in the cluster were insufficient (Figure 1B). Another significant correlating cluster extended bilaterally across the body of the caudate, and included the globus pallidus and the ventral striatum, and also extended bilaterally across the substantia nigra (Figure 1C and 1D). Peak pixels existed in the left substantia nigra at r=0.73, p<.01 (x=-22, y=-44, z=27) (Graph 1), in the body of the right

caudate at r=0.72, $p<.01$ (x=-16, y=22, z=-9), in the ventral striatum at r=0.68, $p<.05$ (x=-9, y=-3, z=1), and in the thalamus at r=0.67, $p<.05$ (x=-9, y=-3, z=1). The parametric images of correlating pixels between the immediate recall version of visual reproduction and D_2/D_3 receptor BP revealed only a single cluster correlation along the right ventral visual stream, with peak pixels reaching r= 0.71, $p<.01$ located at (x=-16, y=6, z=-69) in Talairach space(See Figure 2).. Because all correlations were positive, this means that higher memory scores correlated with greater D_2/D_3 receptor BP in these regions.

Discussion

Implications for results

In this study, we investigated the relationship between measures of neuropsychological functioning among a group of psychiatrically healthy volunteers and either extrastriatal to striatal D_2/D_3 receptor ratios or isolated regional D_2/D_3 receptor densities as measured by PET using [^{18}F] Fallypride. Our data does not support the first of these hypotheses: the ratio approach did not provide superior predictions of verbal or non-verbal immediate recall scores or schizotypal symptoms as assessed with the SPQ. However, even the D_2/D_3 receptor BP of isolated regions produced minimal results when extracted from structurally-delineated ROIs. Our findings suggest that parametric images composed of pixel-cluster correlations between D_2/D_3 receptor BP and other assessments may provide a more sensitive method of investigating potential relationships between baseline D_2/D_3 receptor BP and cognitive performance scores, as it permits the discernment of potential correlations existing in the subregions of various structures that would go unrecognized if they were included in a broader region investigated with ROI

analyses. Furthermore, the parametric images provide visualization of potential correlations between D_2/D_3 receptor BP and cognitive assessments without having to employ preconceptions regarding the relative roles of regional D_2/D_3 receptors in cognition.

In contrast to our hypothesis, significant correlations were not observed between baseline D_2/D_3 receptor BP and schizotypal symptoms, potentially suggesting that D_2/D_3 receptor BP is not associated with such symptoms. This interpretation is tenuous, however, given the paucity of neuroimaging studies that have investigated schizotypal patient populations. Considerable research with animals and schizophrenic patients demonstrates a relationship between D_2 receptors in the striatum and psychopathology, particularly with respect to positive symptoms (Deutch, 1992; Weinberger, 1987; Abi-Dargham, 2004). If our analysis had been conducted with participants who met criteria for a clinical diagnosis of schizotypal personality disorder, or who demonstrated greater variability on sub-scales of the SPQ, we may have observed a relationship between schizotypal symptoms and regional D_2/D_3 receptor BP. Because our participants also underwent a $_D$-amphetamine challenge for another study, any history of psychiatric illness would have excluded them.

In spite of our lack of results concerning ratio analyses and schizotypal symptoms, parametric images did produce significant correlation clusters within isolated regions of the brain between D_2/D_3 receptor BP and performance scores on verbal and visual memory. More specifically, scores on the index of verbal memory showed a significant positive correlation with D_2/D_3 receptor BP surrounding and including regions of the basal ganglia and the substantia nigra, as well as the insula and left temporal pole,

and demonstrated a trend-level association with D_2/D_3 receptor BP in the right hippocampus.

One significant correlation cluster that was observed between D_2/D_3 receptor BP and verbal memory scores included the substantia nigra, the globus pallidus, the body of the caudate, and the ventral striatum. The substantia nigra (SN) possesses reciprocal connections with each region of the striatum (Haber, Fudge, & McFarland, 2000). Although [^{18}F] fallypride does not permit post-synaptic and autoreceptors to be distinguished, prior research has established that the SN consists exclusively of autoreceptors—that is, receptors that are located on the soma, dendrites or axons of DA-containing neurons (Cooper, Floyd & Robert, 1996, chap. 9). Therefore, [^{18}F] fallypride binding in the SN provides an assessment of autoreceptors. When stimulated, autoreceptors inhibit dopaminergic transmission by slowing firing rates, reducing DA synthesis, or decreasing DA release (Cooper, Floyd & Robert, 1996, chap. 9). Therefore, the correlation between D_2/D_3 receptor BP in the SN and verbal memory performance could be interpreted as demonstrating a greater capacity for dopaminergic inhibition within the SN, which possesses numerous feedforward pathways with the striatum. This interpretation is tentative, however. Because the SN consists exclusively of autoreceptors, these results could indicate a greater density of dopaminergic neurons in that region (Olsson**,** H., Halldin, C. & Farde, L., 2004).

Positive correlations between verbal memory scores and D_2/D_3 receptor BP and the body of the caudate offer unexpected results. Although the caudate has been implicated in memory, it has mostly been associated with implicit memory assessments. These results, however, identify a correlation between D_2/D_3 receptor BP in the caudate

and performance on an explicit memory assessment. Future studies are needed to replicate these findings. If supported, this would suggest that the caudate plays a broader role in memory than previously assumed (Cropley, et al. (2006).

The positive correlation between verbal memory and D_2/D_3 receptor BP in the banks of the Sylvian fissure at the left temporal pole also represents an unexpected finding. To my knowledge, no studies have yet reported an association between D_2/D_3 receptors in this region and any dimension of cognitive performance. However, research using fMRI and event-related potential methods have identified activity within this region during the presentation of familiar stimuli (Olson, Plotzker, Ezzyat, 2007). Considering the paucity of research concerning the potential role of D_2/D_3 receptors, or dopamine more generally, within the left temporal poles, this finding provides an intriguing impetus for further research and requires replication.

Although this analysis found only a trend-level association between verbal memory and D_2/D_3 receptor BP observed in the right hippocampus, considerable research identifies a role for hippocampal D_2/D_3 receptors in verbal memory. In a recent PET study using [^{11}C]FLB457, Takahashi et al. (2007), reported a significant correlation between scores on a verbal learning test and D_2 receptor BP bilaterally in the hippocampus. Consistent with the right lateralized findings reported here, Takahashi et al. (2007) observed a greater correlation between verbal memory and the D_2/D_3 BP in the right hippocampus. Kemppainen et al. (2003) also reported a positive correlation between D_2/D_3 BP as assessed with [^{11}C]FLB457 and PET imaging, in addition to reporting reduced D_2 receptor BP in patients with Alzheimer's disease relative to sex- and age-matched controls. The results reported here lend further support to the proposed

relationship between D_2/D_3 receptor BP in hippocampal regions and verbal memory performance.

Finally, the positive correlation observed between D_2/D_3 receptor BP within the ventral visual processing stream and the immediate recall version of visual reproduction poses an interesting consideration. To my knowledge, no studies have identified a role for D_2/D_3 receptors in this region and performance on visual memory, which restricts the interpretations drawn from this finding. However, the absence of any other significant correlation clusters may be more remarkable than the correlation between D_2/D_3 receptor BP and the visual processing stream. Several studies have implicated D_2/D_3 receptors in visuo-spatial memory: Reeves et al. (2005) demonstrate a negative correlation between caudate D_2 receptor BP assessed with [^{11}C] Raclopride and PET imaging and performance on a spatial working memory task. It is possible that D_2/D_3 receptors are not substantially related to performance on the visual reproduction sub-scale of the WMS-III.

Limitations

One of the limitations in interpreting these findings is that the statistical power was poor and may have limited the ability to observe significant associations. Also, neither the PET data nor the cognitive scores were evaluated for gender confounds because doing so would have reduced the degrees of freedom, making it more difficult to observe potential associations. A recent PET study using [^{18}F] fallypride conducted by Ricarrdi et al., (2005) demonstrates sex differences with respect to DA release as measured by BP displacement during a $_D$-amphetamine challenge. More specifically, Ricarrdi et al., (2005) observed a relationship between changes in regional DA release as measured by D_2/D_3 receptor BP and cognition. Sex differences potentially exist with respect to baseline D_2/D_3 receptor BP. This

limitation poses a considerable constraint on the conclusions drawn from this study, and analyses that consider sex differences with respect to baseline D_2/D_3 receptor BP and cognition and psychopathological symptoms offer a compelling direction for future research. Another limitation of this study is that analyses did not control for age as a potential confounding variable; considerable research documents age-related declines in striatal D2/D3 receptor densities (Cropley et al., 2006; Volkow et al., 1998).

Although this study did not observe an association between SPQ scores and D_2/D_3 receptor BP as measured with [^{18}F] fallypride, such results do not necessarily indicate that the two are unrelated. First, although considerable heterogeneity in SPQ scores among both patient and healthy samples have been reported, the participants in this study did not demonstrate considerable variability on sub-scales of the SPQ. They did, however, exhibit sufficient variability on the total score of the SPQ. Although it remains speculative, greater variability across participants on sub-scales of the SPQ may have provided evidence for relative contributions of regional D_2/D_3 receptor populations to specific schizotypal symptoms. For example, Suhara et al. (2002) reported a significant negative correlation between the BP of D_2 receptors in the anterior cingulate and the positive symptom score on the Brief Psychiatric Rating Scale among a sample of schizophrenic patients (BPRS). Because the participants in this study were healthy controls, they may have not provided the sensitivity necessary to detect such relationships. Future analyses that include participants who score in a pathological range may demonstrate a more robust association with D_2/D_3 BP as assessed by [^{18}F] fallypride.

Other potential confounds are related to the neuroimaging analyses conducted in this study. A single participants' MRI scan was used to delineate the ROI boundaries applied to a

composite image of multiple participants' PET scans, and the locations of the pixel-cluster correlations obtained from the parametric images were identified according to a single participants' MRI, which may have skewed the results if the participants' structures were misaligned. Partial volume effects—in which individual differences in the structural composition of both the entire brain as well as specific regions relative to one another—may therefore slightly affect which regions were identified as possessing a relationship with cognitive performance. It is possible that this latter confound may have contributed to the lack of significant correlations obtained from extrastriatal to striatal D_2/D_3 receptor BP ratios. Unfortunately, this confound is difficult to eliminate, as differences in the size and morphology of particular neural structures naturally exist and statistical analyses require consistency between measures. Because the volume of the regions being investigated—whether with ROI extractions or parametric analysis—must be the same across participants, data regarding a potentially informative relationship between structural morphology and receptor expression inevitably becomes discarded. This is of particular concern around the boundaries of the striatum because of the large differences in the D_2/D_3 levels within the striatum and immediately adjacent or proximal brain regions.

Conclusions

A large body of evidence for current models of cortical dopaminergic transmission originates from studies of rodent or non-human primate cortex (Deutch, 1992; Weinberger, 1987). Such studies have shown that lesions applied to entorhinal cortices induce striatal D_2 receptor up-regulation and behavioral deficits that resemble some negative symptoms of SPD and schizophrenia (Schmadel et al., 2004; Schneier et al., 2000). Alternatively, lesions applied to prefrontal cortex increase the responsiveness of receptors in the nucleus

accumbens, which, in the presence of stress, can elicit overt increases in DA release along the mesolimbic pathway and behavioral disturbances that resemble positive symptoms of SPD and schizophrenia (Deutch, 1992; Weinberger, 1987). Given these findings, it seems puzzling that no correlations were observed between D_2/D_3 receptor BP and either the total score or symptom sub-scales of the SPQ. Due to the afore-mentioned confounds that may have restricted this analysis, these findings require further replication before concluding that D_2/D_3 receptor BP is unrelated to schizotypal symptoms.

This study demonstrated significant correlations between verbal memory and D_2/D_3 receptor BP in the basal ganglia, the temporal poles, and the hippocampus, in addition to significant correlations between visual reproduction and D_2/D_3 receptor BP in the ventral visual pathway. It therefore harmonizes with previous research associating D_2/D_3 receptors with cognitive processing (Cropley et al., 2006). Future analyses may benefit from evaluating parametric images depicting pixel-by-pixel correlations between psychopathology and cognitive performance and D_2/D_3 receptor BP rather than ROI analyses. Furthermore, investigations that consider the role of D_2/D_3 receptor BP in the temporal poles and cognitive performance may provide insight into the role of dopaminergic function in these regions.

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Table 1:

	Mean	S.D.	Max	Min
Odd	2.6875	3.400368	13	0
Positive	1.875	2.655184	9	0
Negative	3.0625	4.552929	17	0
Total	7.625	7.623429	26	0

Table 1:

Total and sub-scale scores on the SPQ

Table 2:

	Mean	S.D.	Max	Min
Index Score of auditory memory	105.8823529	13.99054302	138	80
Visual reproduction (Immediate recall)	95.29411765	8.175915131	103	79

Table 2: Scores on sub-scales of Wechsler Memory Scale-III

Table 3:

	Mean	S.D.	Max	Min
Temporal ROI	97.81897966	14.24083933	129.8106114	86.47559859
Lateral Frontal ROI	50.21482132	10.13246562	69.17039045	40.5312263
Cingulate ROI	65.57422003	19.07433338	87.46106069	19
Striatal ROI	2620.367287	297.7265543	3223.805722	2172.488778

Table 3: D_2/D_3 receptor BP of isolated ROIs

Table 4:

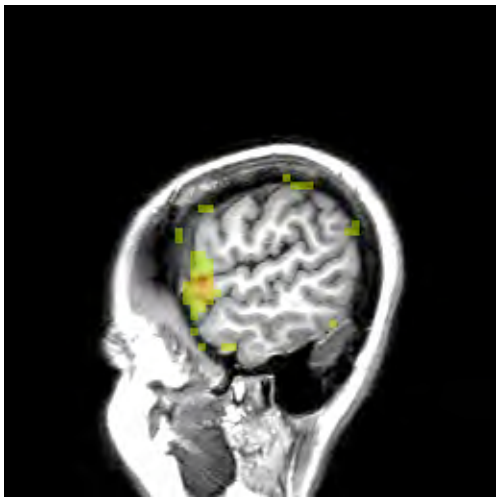
D2/D3 BP of ROIs of extrastriatal:striatal ratios

	Mean	S.D.	Max	Min
Temporal: Striatal	0.02590346	0.0093374	0.0565057	0.02163513
Latfrontal: Striatal	101.27837	0.0048788	0.0299229	0.0136774
Cingulate: Striatal	53.183482	0.004538	0.0335974	0.0189407

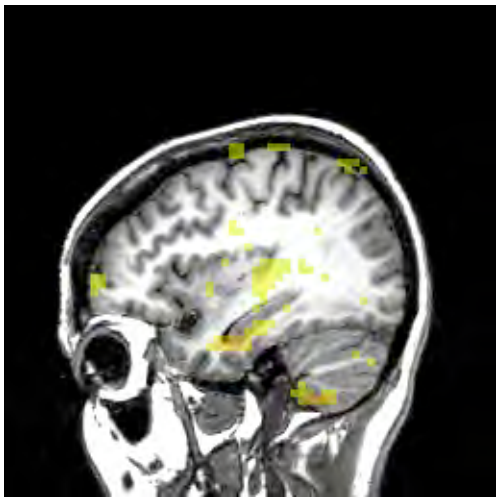
Table 4: D_2/D_3 receptor BP of extrastriatal:striatal ratios

Figure 1:

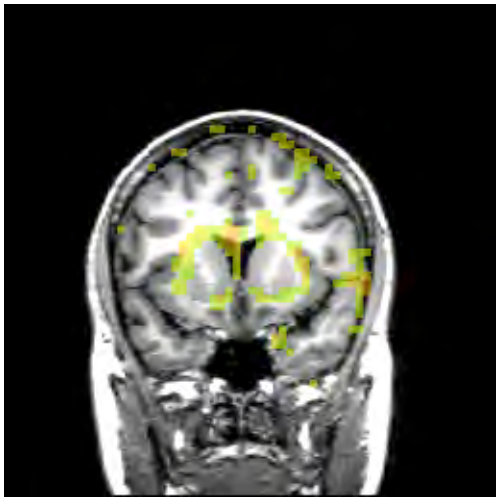
A.



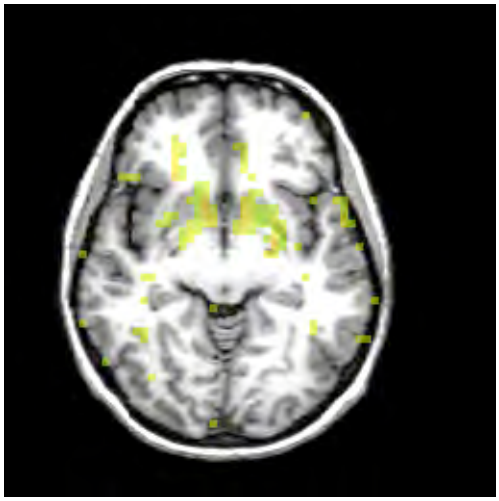
B.



C.



D.



C.

Figure 1: Correlations between Verbal Memory Scores and D_2/D_3 receptor BP

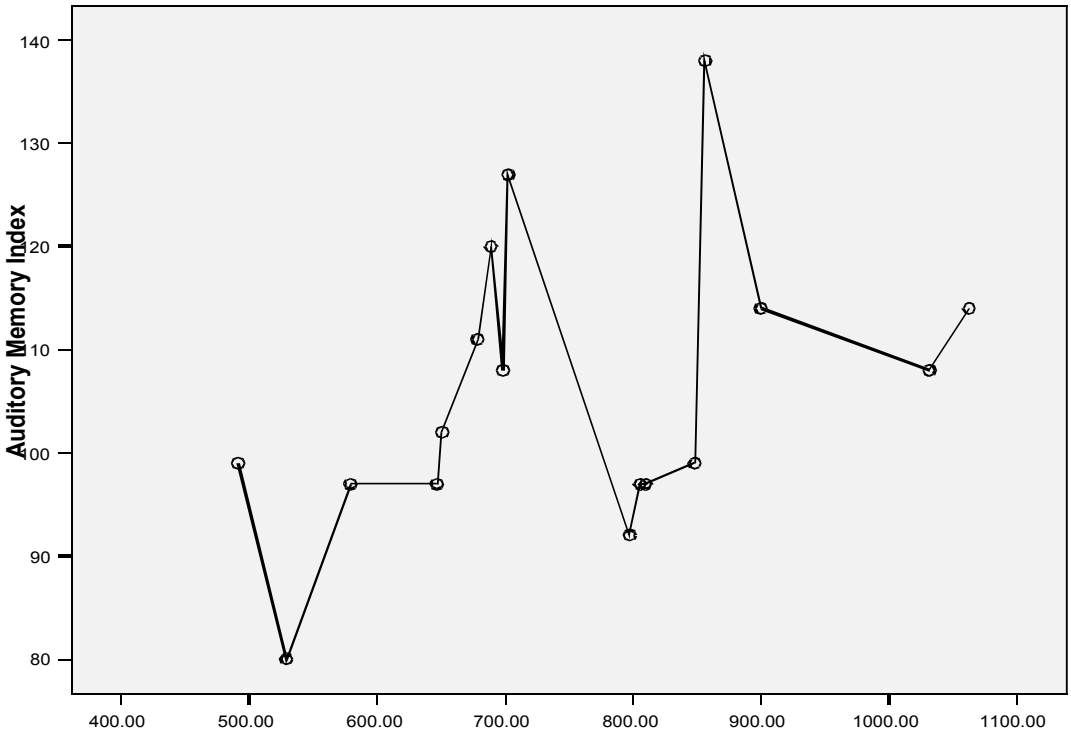
A: Sylvian fissure and Verbal memory

B: Hippocampus and Verbal memory

C: Caudate body, globus pallidus, and substantia nigra and Verbal Memory

C: Ventral Striatum and Verbal Memory (cluster extended from caudate)

Graph 1:


Auditory Memory Index
140
130
120
110
100
90
80
400.00
500.00
600.00
700.00
800.00
900.00
1000.00
1100.00

Graph 1: Correlations between scores of verbal memory and D_2/D_3 BP in the Substantia Nigra (SN)

Figure 2:

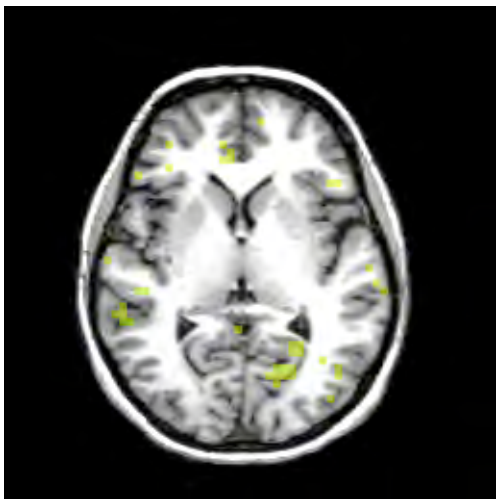


Figure 2: Correlations between Visual Reproduction (immediate recall) and D_2/D_3 receptor BP in the ventral visual processing stream.